REMARKS

This Amendment cancels claims 1-19, 30, 36 and 37, amends claims 20-29 and 31-35, adds new claims 38-50, and presents a substitute abstract. The method steps of claims 20, 22, 24, 28 and 31 are taken from canceled claim 2. The 1.0 wt-%/h minimum dissolution rate feature of claims 20, 22 and 24 is supported by claim 27 as originally filed, while the 2.0 wt-%/h and 4.0 wt-%/h dissolution rates of claims 26, 27, 34 and 47 are supported by page 23, lines 19-22 of the specification. New claims 38-45 correspond to claims 20-27, but specify the method steps of claim 1 rather than claim 2. New claim 48 is taken from original claim 31. The peptide, protein or cell features of claims 46, 49 and 50 are supported by page 13, lines 17-22. Claims 20-29, 31-35 and 38-50 are pending.

This application is subject to a restriction requirement. Claims 20-29, 31-35 and 38-50 correspond to elected Group II, drawn to a bioresorbable SiO_2 monolith, coating or particle.

This application is also subject to an election of species requirement. Claims 21, 29, 33-35, 39, 46 and 47 read on the elected species[1], with each of these claims being generic.

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[1]Applicants elected the species of invention wherein:
A. The specific embodiment is a sol-gel derived SiO_2

This Amendment overcomes the objection to the abstract. More particularly, a substitute abstract is attached which does not contain legal phraseology and which complies with the length requirements for an abstract. Reconsideration and withdrawal of the objection to the Abstract are respectfully requested.

This Amendment overcomes the first objection to claims 21, 27, 29 and 33-35. None of the pending claims depend from a non-elected claim. Reconsideration and withdrawal of the first objection to claims 21, 27, 29 and 33-35 are respectfully requested.

This Amendment also overcomes the second objection to claims 21, 27, 29 and 33-35. All deletions of claim terms in this Amendment are indicated by a strikethrough. Reconsideration and withdrawal of the second objection to claims 21, 27, 29 and 33-35 are requested.

The 35 U.S.C. § 103(a) rejection of claims 21, 27, 29 and 33-35 over the Kortesuo Dissertation (2001) in view of <u>Kortesuo et al</u>., 76 J. <u>Controlled Release</u> 227 (2001) is traversed. The claimed

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monolith, in which

B.(2) A change or changes of sol composition are induced after sol ageing but before gel formation [alternative b)ii in claim 1],

(a) wherein the change or changes comprise the addition of a biologically active agent; and

(b) forced drying of the sol is initiated within 30 minutes from said induced change or changes of sol composition;

C. Wherein the method of forced drying is freeze drying.

bioresorbable sol-gel derived SiO_2 has either a very fast dissolution rate (at least 1.0 wt-%/hour) or a slow dissolution rate (0.001 to 0.05 wt-%/hour). The inventors have discovered a very fast *in vitro* dissolution rate can be achieved by using a combination of specified precursor ratios (e.g., a water to alkoxide ratio of 0.5 to 2.5, and alcohol to alkoxide ratio of at least 0.5), and an initial sol pH of 0.05 to 2.5. A slower dissolution rate can be achieved by departing from these specified precursor ratios.

The cited combination of references fails to raise a *prima facie* case of obviousness against the claimed sol-gel derived SiO_2. Neither the Kortesuo Dissertation nor Kortesuo et al. disclose or suggest a sol-gel derived SiO_2 *in vitro* dissolution rate of at least 1.0 wt-%/hour, or the combination of precursor ratios, pH and drying conditions necessary to achieve such an unexpectedly fast dissolving SiO_2.

Table 2 on page 28 of the Kortesuo Dissertation lists various sol-gel derived SiO_2 monoliths and microparticles which were

prepared using various precursor ratios, pH and drying conditions. None of them had an *in vitro* dissolution rate of at least 1.0 wt-%/hour.

The Kortesuo Dissertation suggests the degradation rate of the silica xerogel can be "modified" by varying the composition of the starting materials, or by varying the manufacturing method from casting to spray drying. Such a statement is merely an invitation to experiment, rather than guidance to one of ordinary skill in the art seeking to prepare a sol-gel derived SiO_2 having a very fast bioresorption rate.

The Kortesuo Dissertation demonstrates the prior art did not understand which factors are decisive to control the dissolution rate of bioresorbable sol-gel derived SiO_2, and how those factors can be managed without detrimentally affecting other properties of the SiO_2 important for many, if not most, applications of bioresorbable sol-gel derived SiO_2. Thus, for example, the Kortesuo Dissertation provides only a very limited possibility of adjusting the dissolution rate of the silica gel of a monolith. In Table 2 (page 28) the dissolution rates obtained using a rather broad pH range of 1-5 resulted in a very narrow degradation rate range of 16.9 to 25.7 %/30 h (0.56 to 0.85 wt-%/h). The

degradation rate range for microparticles is broader, but is still limited to 0.02 to 0.56 wt-%/h.

Similarly, the Kortesuo Dissertation provides only a very limited possibility of adjusting the dissolution rate by adjusting the molar ratio of water to alkoxide. In Table 2, a water to alkoxide ratio range of 6 to 28 resulted in a very narrow degradation rate range of 16.9 to 20.4%/30 h (0.56 to 0.68 wt-%/h). The degradation rate for microparticles is broader, but even here the degradation rate is limited to 0.01 to 0.67 wt-%/h despite using a broader alkoxide ratio range of 6 to 35.

The Kortesuo Dissertation teaches the porosity/surface area and geometry of the sol-gel derived SiO_2 affects its degradation rate. See page 31 ("In general, the porous structure of cast silica xerogel monoliths resulted in a faster...degradation of the matrix as compared to spray-dried particles.") Yet, other factors are often more decisive. See Fig. 2 of Viitala et al., "Adjustably Bioresorbable Sol-Gel Derived SiO_2 for Release of Large Biologically Active Molecules", 36 J. Sol-Gel Sci. & Tech. 147 (2005)(copy enclosed) which shows that despite a much smaller specific surface area (3.4), the degradation rate of monolith Bm12

is clearly <u>faster</u> than that of monoliths Bm11 (ssa of 43), Am03 (ssa of 637) and AM01 (ssa of 697).

In short, the Kortesuo Dissertation fails to disclose or suggest a starting point for correlating the values necessary to produce a sol-gel derived SiO_2 having a specific dissolution rate, as demonstrated by the results listed in its Table 2. In stark contrast, the present application provides such a starting point. The application defines what changes result in slower dissolution rates, and defines the provisos related to having these changes reduce the dissolution rate. See pages 18 to 22 of the application.

The secondary reference does not provide any additional information which would permit one of ordinary skill in the art to arrive at the claimed invention. Reconsideration and withdrawal of the obviousness rejection of claims 21, 27, 29 and 33-35 are respectfully requested.

The provisional obvious-type double patenting rejection of claims 21, 27, 33 and 34 over claims 24, 25 and 30-33 of co-pending, commonly-assigned U.S. patent application S.N. 09/913,643 in view of <u>Kortesuo et al</u>., 76 <u>J. Controlled Release</u> 227 (2001) is

noted. The Examiner is requested to hold this provisional rejection in abeyance until one of the two applications is allowed.

The fees for the new claims and a three month extension of time are being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

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Enclosures:
Petition for Extension of Time
Substitute Abstract
Viitala et al., "Adjustably Bioresorbable Sol-Gel Derived SiO_2 for Release of Large Biologically Active Molecules", 36 J. Sol-Gel Sci. & Tech. 147 (2005)